## REMARKS

### I. Introduction

Receipt of a non-final office action dated July 14, 2004, is acknowledged. In the action, the claims were rejected as allegedly failing to comply with the written description requirement (claims 1-22 and 25-54), and as allegedly indefinite (claims 3, 4 and 15). The claims were also rejected as allegedly not novel over Desieno *et al.*, U.S. Patent No. 5,573,783 ("Desieno") (claims 1, 2, 8-10, 13, 14, 30, 31 and 34-53) or Vernon, PCT Publication WO 95/22318 ("Vernon") (claims 1, 2, 8, 9, 13, 14, 30, 31, 34-38, 41, 42, 45, 46, 49, 50 and 53), and obvious over Desieno, Liversidge *et al.*, U.S. Patent No. 5,145,684 ("Liversidge"), in view of Friend *et al.*, U.S. Patent No. 5,811,388 ("Friend") (claims 1-22 and 25-53).

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

### II. Status of the Claims

In this response, applicants amended claims 1, 3, 4, 30, and 35. Support for the revised claims can be found on page 14, lines 12-17, of the specification (claims 1, 30 and 35) and in the originally filed claims (claims 3 and 4). Upon entry of this amendment, claims 1-22 and 25-54 will be under examination.

### III. Rejection of the Claims Under 35 U.S.C. § 112, first paragraph

Claims 1-22 and 25-54 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the written description requirement. In particular, the claims were rejected because claims drawn to a "nanoparticulate drug [that] has an effective average particle size of less than about 1000 nm, wherein at least 50% of the drug particles have a particle size of less than 1000 nm" is allegedly not supported. The action indicates that without recitation of the phrase "average particle size," the claims are not sufficiently described. Office action at 3.

In the interest of expediting prosecution, applicants amended the claims to recite "an average particle size of less than about 1000 nm." Applicants trust that this amendment renders the rejection moot.

## IV. Rejection of the Claims Under 35 U.S.C. § 112, second paragraph

Claims 3, 4 and 15 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. Specifically, the claims were rejected because it is allegedly unclear whether the phrase "the polymer" refers to a rate controlling polymer or a surface stabilizer.

A skilled artisan would know, based on the teachings in the specification and the clarity of the pending claims that "the polymer" refers to a rate controlling polymer. Nevertheless, in the interest of expediting prosecution, applicants amended claims 3 and 4 to more clearly recite the present invention. Applicants note that claim 15 already specifically recites a rate controlling polymer.

## V. Rejection of the Claims Under 35 U.S.C. § 102

### A. Rejection over Desieno

Claims 1, 2, 8-10, 13, 14, 30, 31 and 34-53 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Desieno. Applicants respectfully traverse this ground for rejection.

According to the examiner, Desieno discloses a pharmaceutical film matrix comprising nanoparticles of a low solubility drug with a steric stabilizer, and over coated with a protective layer, which comprises polyvinylpyrrolidone and polyethylene glycol. Office action at 4. Thus, the examiner contends that the time period of controlled release from about 2 to about 24 hours is inherently taught in Desieno because "Desieno uses the same rate controlling polymer in the over coated protective layer" and "products of identical chemical composition cannot have mutually exclusive properties." Office action at 4. Applicants respectfully disagree with the Examiner's analysis and conclusion.

As provided in applicants' last response, the mere *presence* of a rate controlling polymer, without a correct association with the nanoparticulate drug, will not provide controlled release of the active agent. Indeed, a certain structural relationship must exist

between the nanoparticle and the polymer which provides controlled release. This is not taught in Desieno.

For a feature to be inherent in the teachings of a prior art reference, that feature must "necessarily [be] present in the thing described in the reference and . . . be so recognized by persons of ordinary skill." M.P.E.P. § 2131.01(III), quoting *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264 (Fed. Cir. 1991). This standard of inherency is not met by Desieno.

Specifically, the polyethylene glycol and polyvinylpropylene coatings mentioned as examples in Desieno "provide[] improved stability to the pharmaceutical composition" (Desieno at col. 5, lines 3-4). Therefore, Desieno does not teach or suggest adding a rate controlling polymer to obtain a controlled release composition. "Stability" is not the same as "rate controlled," as a "stable" composition can be an immediate release composition. Thus, a time period of controlled release from about 2 to about 24 hours, required by Applicants' claims, is not "necessarily and always present" and therefore, not inherently taught in Desieno.

Therefore, for at least these reasons, Desieno does not teach every element of the claimed invention and therefore withdrawal of this ground for rejection is respectfully requested.

**B. Rejection over Vernon**

Claims 1, 2, 8, 9, 13, 14, 30, 31, 34-38, 41, 42, 45, 46, 49, 50 and 53 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Vernon. In particular, the claims were rejected because "Vernon discloses a controlled release formulation comprising microspheres matrix made of polymer . . ., the microspheres are over coated with a copolymer to provide a controlled release over a period of days or even weeks." Office action at 5. Applicants respectfully traverse this ground for rejection.

Vernon does not teach each and every element of the claimed invention. Vernon is directed to a drug delivery system, and a controlled release formulation in a microspherical form, in particular. Vernon describes that "[t]he particle size of the precipitate is in the order of 100 nm to 100 μm" (Vernon at col. 8, lines 23-25). This teaching does not disclose

Applicants' claimed effective average particle size of less than about 1000 nm. Further, there is no indication in Vernon to prepare a nanoparticulate agent as a controlled release formulation.

As such, Vernon fails to teach, either expressly or inherently, a nanoparticulate agent with an effective average particle size of less than about 1000 nm, in combination with a surface stabilizer and a rate controlling polymer. Thus, Vernon does not anticipate the claimed invention.

## VI. Rejection of the Claims Under 35 U.S.C. § 103

Claims 1-22 and 25-53 were rejected under 35 U.S.C. 103(a) as allegedly obvious over Liversidge and Desieno in view of Friend. According to the examiner,

> It would have been obvious for one of ordinary skill in the art to modify the nanoparticle of Desieno and Liversidge using the excipients and enteric coating polymers in an effective amount in view of the teachings of Friend, because Friend teaches a tablet dosage form suitable for controlled release of poorly soluble drug substance.

Office Action at 7. Applicants respectfully traverse this ground for rejection.

The cited art does not establish: (1) some suggestion or motivation to modify the reference or to combine reference teachings, (2) a reasonable expectation of success, and (3) that the prior art references, when combined, teach or suggest all the claim limitations to establish a *prima facie* case of obviousness. *See* MPEP §2143 (Aug. 2001). "Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991).

Liversidge describes a polymer that is associated with the surface of an active agent that acts to minimize agglomeration due to interparticle attractive forces (*i.e.*, a surface stabilizer). The compositions in Liversidge have an effective average particle size of less than about 400 nm and are formulated to increase bioavailability to the tissues after administration. Liversidge, however, does not disclose the addition of a rate-controlling polymer to the pharmaceutical composition, nor does this reference teach controlled release compositions.

Likewise, Desieno does not teach the addition of a rate controlling polymer to obtain a controlled release composition. Desieno merely describes a film matrix comprising nanoparticles, a steric stabilizer, a film dispersing agent coated on the surface of carrier particles, and overcoated with a protective layer. As described in this reference, the steric stabilizer "ha[s] steric stabilizing properties" (Desieno at col. 3, lines 49-50), the film dispersing agent "are those materials which oppose the binding capability of the film" (Desieno at col. 4, lines 27-29), and the protective layer "provides improved stability to the pharmaceutical composition." (Desieno at col. 5, lines 3-4). But Desieno also does not disclose the addition of a rate controlling polymer so as to obtain a controlled release composition.

The deficiencies in these teachings cannot be rectified by Friend because there is no suggestion or motivation to modify Desieno or Liversidge, or to combine them with the teachings in Friend. In fact, Friend relates to pharmaceutical compositions for delivering a therapeutically effective amount of a drug to the gastrointestinal tract, especially to the colon. Friend describes the challenges of providing drugs that would pass through the upper gastrointestinal tract without degradation and addresses this by providing pharmaceutical formulations with a specified amount of hydrocolloid. Friend, however, does not teach or recognize the value in preparing a nanoparticulate composition that has an effective average particle size of less than about 1000 nm in a controlled release formulation.

Nanoparticulate compositions are formulated to obtain fast, immediate release of the active agent to obtain an increase in bioavailability, *i.e.*, increase the availability of the drug to a tissue after administration. It would be counterintuitive to prepare such a pharmaceutical composition in a controlled release formulation and therefore, there is no explicit or implicit teaching to combine the cited references.

## VI. CONCLUSION

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and arguments.

The present application is now in condition for allowance. Early notice to that effect is earnestly solicited.

The examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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